SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL

MEETING

December 8, 2006

Hilton Washington D.C. North
Gaithersburg, Maryland

Circulatory System Devices Advisory Panel Meeting

December 8, 2006

Attendees

Chairperson
William H. Maisel, M.D., M.P.H.
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Voting Members
Sharon-Lise Normand, Ph.D.
Harvard School of Public Health
Boston, Massachusetts

Richard L. Page, M.D.
University of Washington School of Medicine
Seattle, Washington

John C. Somberg, M.D.
Rush University Medical Center
Lake Bluff, Illinois

Christopher J. White, M.D.
Ochsner Clinic
New Orleans, Louisiana

Clyde W. Yancy, M.D.
Baylor University Medical Center Dallas
Dallas, Texas

Consultants
Jeffrey A. Brinker, M.D.
The Johns Hopkins Hospital
Baltimore, Maryland

Michael J. Domanski, M.D.
National Institutes of Health
Bethesda, Maryland

L. Henry Edmunds, Jr., M.D.
The Hospital of University of Pennsylvania
Philadelphia, Pennsylvania

Robert Harrington, M.D.
Duke Clinical Research Institute
Durham, North Carolina

John W. Hirshfeld, M.D.
The Hospital of University of Pennsylvania
Philadelphia, Pennsylvania

Norman S. Kato, M.D.
Cardiac Care Medical Group
Encino, California

Warren K. Laskey, M.D.
University of New Mexico School of Medicine
Albuquerque, New Mexico

JoAnne Lindenfeld, M.D.
University of Colorado Health Science Center
Denver, Colorado

Douglas Morrison, M.D.
University of Arizona
Tucson, Arizona

Steve Nissen, M.D.
Cleveland Clinic Foundation
Cleveland, Ohio

Eric Topol, M.D.
Case Western Reserve Foundation
Cleveland, Ohio

George Vetrovec, M.D.
Medical College of Virginia, VCU
Richmond, Virginia

Judah Z. Weinberger, M.D.
Columbia University
New York, New York

Industry Respresentative
Pamela W. Adams
Senior Vice President, ETEX Corporation
Cambridge, Massachusetts

Consumer Representative
Linda A. Mottle, M.S.M., R,
GateWay Community College
Phoenix, Arizona

Executive Secretary
James P. Swink
Food and Drug Administration
Rockville, Maryland

FDA Participants
Geretta Wood
Director, Advisory Panel Program

Bram Zuckerman, M.D.
Director, Division of Cardiovascular Devices

Ashley Boam

Daniel Schultz, M.D.
Director, CDRH

CALL TO ORDER

Panel Chairperson William H. Maisel, M.D., M.P.H., called the meeting to order at 8:05 a.m. and asked the panel members to introduce themselves. **Geretta Wood, Director, Advisory Panel Program,** read the conflict of interest statement. Waivers have been granted to Robert Harrington, JoAnne Lindenfeld, Richard Page, George Vetrovec, and Clyde Yancy. Ms. Wood noted that Judah Weinberger no longer has a financial interest requiring a conflict of interest waiver.

DISCUSSION OF BROADER USE OF DES AND ITS IMPLICATIONS

FIRST OPEN PUBLIC HEARING SESSION

Alexandre Abizaid, M.D., Ph.D., Instituto Dante Pazzanese de Cardiologia, Sao Paulo, talked about the Heart Hospital and Dante Pazzanese Registry on drug-eluting stents (DES) and about the possible mechanism of late thrombosis. Stent thrombosis occurred in 1.3% of patients. Intravascular ultrasound (IVUS) observations suggest that late acquired incomplete apposition may be one of the most important mechanisms of subacute stent thrombosis (SAT).

Roxana Mehran, M.D., Columbia University Medical Center, discussed the MATRIX prospective all-comers single arm study or registry in complex patients. Frequency of early and late adverse events is low and similar to those reported for simple low-risk lesion patients. Overall incidence of stent thrombosis using the expanded definition was 1.2% or 2% when the possible is included. Higher rates of important events are seen in patients with more complex lesions.

David Kong, M.D., Duke University Medical Center, presented results from the Duke Cardiovascular Diseases Data Bank looking at long-term clinical outcomes for

patients receiving drug-eluting and bare metal stents (BMS) and at clopidogrel use beyond six months. Compared to bare metal, DES are associated with reduced rates of target vessel revascularization (TVR). Death and non-fatal myocardial infarction (MI) were higher for DES patients who stopped clopidogrel after six months.

Ralph Brindis, M.D., and **David Magid, M.D., M.P.H., Kaiser Permanente,** presented Kaiser data on DES use from Colorado and San Francisco. DES implanted outside of current FDA indications are associated with increased risk of adverse events. Clopidogrel may be associated with reduced adverse outcomes in the one to six months past the current recommendation, but there is no significant protective effect thereafter.

David O. Williams, M.D., Rhode Island Hospital, presented data from the DEScover Registry and the Dynamic Registry. He concluded there was no signal of excess death or MI among DES patients; there was substantial reduction in TVR rates; off-label outcomes were worse than on-label; and bare metal off-label patients fared worse than on-label DES patients.

Gregory Mishkel, M.D., Prairie Heart Institute, discussed Prairie's real-world DES database. The total unadjusted rate of stent thrombosis over three years is 1.9 percent, but the unadjusted rate of definite and probable is only 1.1 percent. Cumulative definite event rate is .45 percent per year after the firs thirty days. Dr. Mishkel said that possible stent thrombosis is an overly sensitive and non-specific indicator. Late and very late stent thrombosis suggests etiologies other than discontinuation of antiplatelet therapy.

Ron Waksman, M.D., Washington Hospital Center, presented results from contemporary registries at the hospital. They found stent thrombosis was higher in off-

label DES use. Dr. Waksman stated the ARC definition should be modified. Careful patient selection is crucial, and off-label use should be reconsidered or restricted. He recommended that diabetic patients with multi-vessel disease should be referred to surgery.

Dr. White asked Dr. Waksman about on and off-label use of both drug eluting and bare metal stents. Dr. Waksman said in general for both on and off-label use, DES are more thrombogenic than BMS. He said this was different than the data presented by Dr. Mishkel.

Dr. Somberg asked Dr. Williams for longer than one year follow-up from the registry started in the late 1990's. Dr. Williams said there was only five-year data on a small cohort of BMS patients but they are seeking funds to do further follow-up.

Dr. Topol asked Dr. Kong about the discrepant finding of the recent JAMA paper that showed DES patients on clopidogrel doing the best of the groups and about any analysis of on-label versus off-label use. Dr. Kong said they had not analyzed on-label versus off-label. He said the leading hypothesis for the lower event rates for DES with clopidogrel is that the antiplatelet therapy reduces the likelihood of late thrombotic events and that even for BMS patients there was a non-significant 23 percent relative reduction in mortality associated with extended clopidogrel use. Dr. Topol pointed to the stark difference compared to the Swedish registry discussed the previous day and noted a lot of Dr. Kong's analysis was adjusted. Dr. Kong said one issue is that even in randomized clinical trials there is often a mixture of patients using clopidogrel for extended durations and those who are not, and this may account for different conclusions reached when analysis is done based on stent type rather than using landmark parameters.

Dr. Maisel congratulated Dr. Kong for highlighting limitations of his data, particularly the recall bias associated with patients' use or memory of use of clopidogrel and the lack of detailed data on bleeding complications associated with clopidogrel. He asked Dr. Kong if there was sufficient data to make a recommendation on duration of clopidogrel use. Dr. Kong said it was yet to be determined but thought it reasonable to accept the AHA recommendation of 12 months as a minimum.

Dr. Normand asked about patients who did not report their medication use being excluded from the analysis, and Dr. Kong said approximately eight percent of patients were excluded for that reason. Dr. Normand then asked Dr. Mishkel for information about why CYPHER versus TAXUS stents are used by interventionists. Dr. Mishkel discussed factors related to availability of one versus the other and suggested that continued preponderance of CYPHER stent use may reflect marketing practices or a desire to use a product with a longer track record. Dr. Normand inquired further about differences in patient characteristics between the two stents. Dr. Mishkel said that although statistically significant the differences were unlikely to be clinically significant. He also said there is a general belief that in tough anatomical subsets TAXUS may be more deliverable.

Dr. Yancy asked Dr. Kong about adherence to other medical therapies in his patient population. Dr. Kong said they had only looked at aspirin and there was a high correlation between use of clopidogrel and aspirin. Dr. Yancy suggested looking at beta blockers, ARVs, and ACE inhibitors would have been helpful and asked if they had looked at a data cut for left ventricular dysfunction, and Dr. Kong said they had not.

Dr. Yancy asked if MATRIX would look at possible gender or ethnic group differences with regard to adherence to antiplatelet therapy. Dr. Mehran said there is less adherence and follow-up in the minority population, especially immigrants.

Sanjay Kaul, M.D., Cedars-Sinai Medical Center, gave a presentation on work done with his collaborator George Diamond, M.D. on balancing the risks and benefits of DES. He made four regulatory recommendations. With regard to approval, there should be larger and longer pre-approval randomized clinical trials (RCTs) that have patients representative of the real world, hard clinical endpoints, and are adequately powered, and there should be post-approval device registries with extended follow-up and greater public access to data. The operational recommendations are for explicit standards of evidence and universal criteria adopted by the principle stakeholders. Administrative recommendations are for comprehensive post-marketing surveillance, balancing private and public needs, incentives to encourage compliance and education, and consistent public policy. Additional recommendations are for therapeutic, tort, and fiscal reform.

Jeffrey W. Moses, M.D., Columbia University Medical Center, provided his perspective on DES as a practicing interventional cardiologist. He recommended a more considered use of DES including careful scrutiny of a patient's ability to adhere to antiplatelet therapy. He said much larger clinical trials with longer follow-up are needed. New DES technologies may reduce safety concerns.

Peter K. Smith, M.D., Duke University, talked about the relative merits and clinical selection of coronary artery bypass grafting (CABG), BMS, and DES. He said that the significant benefit of CABG over stenting has been demonstrated and appears to

increase with increasing follow-up. He concluded by saying that the purported unmet need being served by off-label stent use is already met by CABG.

Robert A. Guyton, M.D., Emory University School of Medicine, talked about the history of evidence-based coronary revascularization. He said there is need for comprehensive databases of multi-vessel disease therapy, but stated that DES are inferior to coronary bypass in multi-vessel disease. He said the labeling should specifically include multi-vessel disease patients in the list of subgroups in which safety and effectiveness have not been demonstrated.

T. Bruce Ferguson, Jr., M.D., Brody School of Medicine at ECU and Society of Thoracic Surgeons, provided the panel with the Society's perspective. He recommended a multidisciplinary patient-centric disclosure prior to intervention and that FDA form partnerships with professional societies for the purpose of information collaboration and the formation of robust, comprehensive databases.

Timothy Henry, M.D., Director of Research, Minneapolis Heart Institute Foundation, discussed the impact of DES in ST-elevation MI (STEMI) in the Institute's Level 1 MI Program. He concluded that DES reduce all-cause mortality as well as MACE compared to BMS, but stent thrombosis is slightly higher, particularly in the paclitaxel group and predominantly after one year.

Jim Gustafson, M.D., Possis Medical, spoke about use of DES in patients with thrombosed coronary lesions. The pre-clinical and real world experience supports the conclusions that presenting thrombus complicates PCI, unresolved presenting thrombus negatively affects DES drug delivery, and Angio-Jet thrombectomy can be used to turn a high-risk off-label lesion into a lower risk, on-label use for DES.

Robert S. Hillman, Ph.D., Accumetrics, Inc., talked about appropriate dose, timing, and duration of clopidogrel therapy for DES and the use of VerifyNow, an approved point-of-care assay for monitoring platelet function. The level of platelet inhibition at PCI has clinically relevant impact on outcome, but even with appropriate administration of clopidogrel platelet inhibition is suboptimal in a large proportion of patients. Platelet inhibition monitoring will yield insights into appropriate administration.

Dr. Edmunds asked Dr. Ferguson about operative mortality for CABG. Dr. Ferguson said the overall risk-adjusted 30-day mortality is in the range of 1.95 percent based on a national representative sample from over 700 hospitals and just under one percent for elective cases which are predominantly multi-vessel disease.

Dr. Lindenfeld asked Dr. Kong about the 20 percent difference in aspirin use at six months in patients on versus off clopidogrel. Dr. Kong said there was high correlation between clopidogrel and aspirin therapy and recommended dual antiplatelet therapy.

Dr. Page asked Dr. Henry if the Angio-Jet was used in any acute MI patients, but Dr. Maisel informed him that Dr. Henry was no longer present. Referring to the low mortality of CABG, Dr. Page then asked Dr. Ferguson what the absolute benefit was. Dr. Ferguson replied 4.6 percent over three years.

Dr. Laskey asked why Dr. Kong's reported frequency of stent thrombosis was so different than those reported by Drs. Mehran and Mishkel. Dr. Kong said that real-world data is often less clear than randomized controlled data. He also reiterated that his analysis looked at all-cause death and non-fatal MI as opposed to stent thrombosis as defined by ARC. Dr. Kong said the fact that the absolute proportions of those reporting

death or non-fatal MI were higher than reported in randomized trials may reflect a broader population, less patient selection, and potentially higher patient risk subsets.

Dr. Laskey next asked Dr. Mehran to explain the differences. Dr. Mehran noted that MATRIX has incomplete two-year follow-up while Dr. Kong has three years. She also said there is a lack of understanding of aspirin, clopidogrel, and bleeding issues.

Dr. Morrison asked Dr. Guyton about the possibility of correcting for the limitations of registries and wondered how sure he was given those limitations that CABG prolongs life. Dr. Guyton said a robust comprehensive should be developed and should include anatomic predictors of success. He said they currently do the best they can with propensity analysis of the available fields.

Rick Kuntz, M.D., M.Sc., Medtronic, Inc., talked about Medtronic's Endeavor stent. He stated that there is too much variability in DES with respect to platform, polymer, and drug used to consider them a class. The data available on Endeavor demonstrates prevention of restenosis without increased safety risk, and Medtronic is committed to ongoing follow-up as well as large randomized studies to look for new signals.

Krishna Sudhir, M.D., Abbott Vascular Cardiac Therapies, talked about Abbott's XIENCE V drug-eluting stent. He stated that it has a well-studied bare metal platform, pre-clinical data has shown good endothelialization and limited chronic inflammation, and SPIRIT I and II have shown superior efficacy and encouraging safety data.

Laura Mauri, M.D., M.Sc., Chief Scientific Officer, Harvard Clinical Research Institute, and Interventional Cardiologist at Brigham and Women's

Hospital, presented data for several DES trials involving a common drug and polymer. She concluded that the type of prespecified combined safety analysis described is a method that could be performed at varying durations of follow-up, yields greater precision with regard to safety, could identify predictors with greater certainty, and could increase power to detect if a consistent effect was attributable to a specific drug polymer combination.

Dr. Somberg asked Dr. Kuntz about the antiplatelet therapy recommendation and protocol requirements in the ENDEAVOR studies. Dr. Kuntz said all the ENDEAVOR studies used a requirement of three months. He said the future PROTECT study would have a 6 month requirement to compare against another stent with a six month requirement. Dr. Zuckerman asked Dr. Kuntz if he would reconsider that based on data presented at the meeting. Dr. Kuntz said he was unsure there is enough evidence to extend antiplatelet therapy in the type of patients studied in the randomized studies, but he agreed it would be good to reconsider something longer for PROTECT since it will look at a broader group of all-comers.

Dr. Normand asked Dr. Kuntz whether stent choice was really driven primarily by availability. Dr. Kuntz said that historically they had been viewed as exchangable, particularly with regard to prevention of restenosis and safety of the devices but thought that would be less true going forward given differing perceptions about performance and delivereability. Dr. Normand inquired further about region and patient characteristics. Dr. Kuntz thought people would try to determine which stent was the best overall and adopt it. Dr. Normand asked Dr. Mauri about the apparent contradiction between her plan to use a hierchal model and her belief that the stents are not exchangeable. Dr.

Mauri said exchangeability refers to whether from the standpoint of the drug and polymer they can be considered a class.

Dr. Normand then asked if the greater precision for survival modeling was in regard to overall rates for all stents or for each study. Dr. Mauri said she was mainly referring to the drug/polymer combination and said it would be valuable to find a signal common to the combination. Dr. Normand liked the idea and said it was good that the overall estimate would have inflated confidence intervals and that the individual studies would have more precision.

Dr. Yancy asked Dr. Sudhir if in designing the stent different doses or methods of eluting the everolimus so as to prevent downstream consequences. Dr. Sudhir stated that everolimus has slightly lower potency than sirolimus and thus they are already using a lower dose but agreed it was important to determine if what is being seen is some sort of drug-dependent dose-related toxicity. Dr. Yancy noted that everolimus has not been used for heart transplant recipients because of toxicity concerns.

Dr. Harrington asked Dr. Mauri if individual sponsors had signed off on the plan to combine data and agreed to share their data with the other sponsors. Dr. Mauri said it would not be necessary for them to share data with one another as an independent analysis could be done by a central CRO. Dr. Harrington inquired what data would then be given to the individual sponsors. Dr. Mauri said she did not think there would be any intention to share data unless all sponsors involved agreed to it. She said the idea was still just a proposal.

Dr. Laskey asked Dr. Kuntz if he would continue to pursue establishing the link between stent thrombosis and death MI and about the downstream benefit and preventing

restenosis. Dr. Kuntz said the link is pretty straightforward but said it could be just an issue of signal to noise ratio. He also said only a small portion of restenoses are associated with death or MI and changes in stent thrombosis overall will have a larger impact. He said that if safety can be improved while maintaining reductions in revascularization then you'll likely start to see a signal in the death and MI rate.

INDUSTRY CLARIFICATIONS

Dennis Donohoe, M.D., Cordis Corporation, said they had not been able to determine exactly how to replicate the analysis presented by Dr. Baim and instead presented a similar analysis based on Dr. Stone's presentation on the same issue. He said the rates were fairly comparable between CYPHER and bare metal in a subset looking at reasons for morality and MI extending out of those who had stent thrombosis or a TLR. Referring to discussion about FDA including observational data from registries in the labeling, Dr. Donohoe said they have other data, including randomized, non-randomized, and registry data, some independent of Cordis, looking at mortality and MI out to three or four years.

Donald S. Baim, M.D., Boston Scientific Corporation, said that product labels are not static and can be changed following label expansion studies. He said the real-world data continues to be supportive and said Boston Scientific awaits new indication expansion trials such as SYNTAX.

Dr. Maisel asked why Cordis had not provided any registry data out past one year. Dr. Donohoe said the protocol for the condition-of-approval study was approved with one year of follow-up. He said two Japanese registries are underway and are being

extended. Based on his recollection that the panel had been concerned about years of follow-up, Dr. Maisel asked Dr. Zuckerman to comment. Dr. Zuckerman began by saying there is always balance between getting all the data we would like and doing something reasonable to answer questions about safety. He said that at the time, based on the model of BMS, they were primarily concerned about stent thrombosis in the one year timeframe. Dr. Zuckerman also stated that additional post-approval can still be done with the sponsors.

Dr. Somberg said the panel had been concerned not with late stent thrombosis but with long-term durability of the stent. Dr. Zuckerman said they are dealing with new technology that has transformed interventional cardiology and said adjusting post-approval strategies could be a legitimate recommendation of the panel. Dr. Domanski did not think it fair to consider this issue a criticism of the FDA or sponsor especially since the longer time period was discussed based on an issue that turned out not to be of concern. Dr. Maisel said it is incumbent on everyone involved to get a better understanding of long-term implications of a therapy that will be implanted in millions of patients and remain in them for the rest of their lives. Dr. Domanski said if that had been the original rationale it might have been more compelling.

Dr. Nissen reminded everyone of the value of independent registries and suggested they may be more objective. Dr. Somberg noted that data from sponsors is extensively reviewed by FDA and expressed reservations about the data presented at the meeting not having been subjected to the same scrutiny, particularly OUS data given a paper on possible differences in the generic clopidogrels used in Europe. Dr. Zuckerman said that it is a challenge to quickly initiate condition of approval studies and sponsors

should work on post-approval with FDA during the PMA review so that studies or registries can be ready to roll out. Dr. Normand argued strongly in favor of including a control group in mandated registries so that patients can have information to compare to alternatives. Dr. Donohoe stated that Cordis moved to support other registries when questions about long-term safety came up.

SECOND OPEN PUBLIC HEARING

James T. Dove, M.D., President-Elect, American College of Cardiology, presented the ACC's recommendation of three strategies, to reiterate patient selection and determine the best treatment, to reiterate that the approval indications were for small, select subsets of patients, and to gain a better understanding of outcomes in complex patients.

Gregory J. Dehmer, M.D., President, Society for Cardiovascular Angiography and Interventions, made the following recommendations on behalf of SCAI: physicians should adhere to established guidelines for PCI, we should determine if patients are appropriate candidates for DES, DES must be implanted properly, and there should be increased patient and physician education regarding DES. Unresolved issues include the incidence of stent thrombosis with DES, the role of drug resistance, and what to tell patients with drug-eluting stents.

Frederick Grover, M.D., President, Society of Thoracic Surgeons, urged the panel to focus on the broad picture of the multiple options for treatment of patients with ischemic heart disease. He said that off-label use of DES, particularly in multi-vessel disease, is a major public health problem causing unnecessary deaths and offered the following recommendtions: to change the labeling to reflect that safety and effectiveness

of stenting in multi-vessel disease has not been established, adequate informed consent regarding all treatment options by a multidisciplinary team prior to intervention in multi-vessel disease, robust comprehensive databases to assist in determining appropriate therapy in various patient subsets, and stronger partnerships between FDA, professional specialty societies, and industry working to deliver better and safer patient care.

Sidney C. Smith, M.D., American Heart Association, provided the AHA's current recommendations for patients undergoing PCI. He noted that the number of patients affected by stent thrombosis is small and said the important research questions remaining are refined selection criteria, technical approaches for complex interventions, proper duration of antiplatelet therapy, and methods to promote good communication in clinical decision-making.

Mark A. Turco, M.D., Washington Adventist Hospital and Uniformed Services University of the Health Sciences, discussed the history of interventional cardiology as it pertains to the day's discussion. He concluded that risk and benefits of DES must be weighed and said the benefits are clear and the risks quite small, the role of DES in late stent thrombosis needs to be understood, any safety issue must be resolved first while preserving efficacy, and DES technology must continue to advance.

Ryszard Rokicki, Electrochemist, spoke about his process of magneto-electropolishing for improved bio and heamocompatibility of metallic surfaces in the context of bare metal stents through improved surface wetability. He suggested that this increased wetability may be favorable to faster and more perfect endothelialization and minimization of in stent restenosis. He challenged stakeholders to rethink DES programs and work on improving BMS to benefit patients and reduce costs.

Rick Dulin, DES patient, talked about his experience as a subject in the SPIRIT III trial and his fear upon learning of the potential risks of his stent in the media. He recommended that information be provided in a culturally acurate, linguistically diverse, and appropriate literacy level for the millions of Americans potentially impacted by their DES and that support services be provided. He concluded by urging the panel to help alleviate patient concerns and fears if the stents are performing as intended.

Ms. Mottle said she was heartened by the persistence in obtaining the most relevant and real world safety and efficacy data and that there is still a need for more data. Outstanding issues include selection criteria for higher risk patients and true informed consent for patients.

Dr. Domanski asked Dr. Smith the rationale for stopping clopidogrel therapy at twelve months. Dr. Smith said CURE and CREDO had led to a discussion of nine to twelve months and they decided if there weren't any problems it would be desirable to continue for a year. He said they still do not know the significance of a small incidence of late stent thrombosis and how they might approach it. Dr. Domanski asked if he meant they might have to reconsider the timeframe for clopidogrel. Dr. Smith said that was correct but cautioned that the ACA/AHA guideline group would have to look at all the data presented at the meeting.

Dr. Harrington asked Dr. Smith if the AHA would make recommendations regarding choice of bare metal versus drug-eluting stents. Dr. Smith said that AHA together with ACC and SCAI would if the evidence is there and suggested it might be likely particularly with regard to certain clinical conditions.

FDA QUESTIONS TO THE PANEL

Dr. Zuckerman said that although FDA and HHS do not typically extensively regulate the practive of medicine, there are signals that need to be looked at which the agency cannot ignore. He said FDA could work after the meeting on whether the panel's recommendations should be included in the labeling or some other type of notification.

3. The pivotal randomized trials of CYPHER and TAXUS submitted for FDA approval primarily involved use of DES in non-complex patients and lesions. Following these approvals, it is estimated that a majority of DES are implanted in lesions outside of their current indications for use, such as in-stent restenosis lesions, bifurcation lesions, coronary artery bypass grafts, acute myocardial infarction, chronic total occlusions, overlapping and multiple stents per vessel and in patients with multivessel disease and chronic renal insufficiency. Given currently available data, are there safety concerns regarding stent thrombosis, death, and myocardial infarction rates for DES use in these complex patients and lesions?

a. If so, can lesion subsets or patient populations at a particularly higher risk of DES thrombosis within the "off-label" patient population be identified?

Panel members tended to think there are potential safety concerns in complex patients and lesions. However, improvement in restenosis may mitigate increased risk of stent thrombosis. There were concerns about the state of the evidence. One panel member thought CABG was a better comparator for off-label uses than BMS. Another suggested that the Swedish registry may have been misrepresented in terms of whether there was a significant difference. Yet another proposed the possibility that off-label uses should be contraindicated.

Dr. Maisel asked if anyone disagreed with the statement that off-label use of DES is associated with higher risk of stent thrombosis, death, and MI compared to on-label use of DES. A panel member disagreed and said any differences are likely confounded by the different patient populations, and Dr. Maisel said that was precisely the point. Another member suggested including BMS in the proposed statement. Dr. Maisel agreed it was likely to be true for BMS but did not think enough data had been presented on

BMS. Responding to criticism of establishing a cause and effect relationship, Dr. Maisel altered the statement to be that less good outcomes are observed in patients in whom a DES is used off-label compared to on-label.

Dr. Maisel then asked if there was adequate data to say anything about comparing DES to BMS or CABG in the off-label population. Panel members generally agreed that CABG was a more appropriate comparison. Dr. Maisel then asked if there was any off-label use that the panel found acceptable. A panel member said a better question that would drive clinical practice is are there any off-label uses that should not be done and suggested there were issues with bifurcation. A panel member said there was currently no basis for adding any off-label uses to the label or for proscribing any off-label use. Another member said that some patients have been turned down for surgery and pointed out that the surgical outcomes presented were not for the highest risk subgroups. One panel member said one of the problems was in pooling together all off-label patients, many of whom have benefited out to three or four years. Another said there was insufficient data to make any such determination. One panel member said one subgroup that should be emphasized is anyone unable to understand, afford, or comply with antiplatelet thereapy. Dr. Maisel took issue with excluding patients who cannot afford medications and suggested defining it as anyone who is not expected to be able to continue their medication for the prespecified duration.

Dr. Maisel stated that rates of stent thrombosis, MI, and death are higher when DES are used off-label as compared to on-label. With regard to part (a), he said there are concerns about those issues discussed but there is not data to change the label or make any broad recommendation.

b. Among the "off-label" population, would the antiplatelet therapy modifications discussed previously for on-label use apply differently to this population or include other patient subgroups?

The panel generally agreed on one year of antiplatelet therapy for off-label use of DES in patients at low risk of bleeding. Some panel members were uncomfortable with changing current guidelines. One panel member said the guideline of one year was not really based on any data. Dr. Zuckerman agreed that there continues to be uncertainty and asked if the current guidelines were a step forward with the caveat that they will be updated as more data becomes available. Dr. Maisel asked if anyone felt there should not be twelve months of antiplatelet therapy, and none responded.

c. If DES thrombosis concerns regarding more complex lesions or patient subsets have been identified, do they apply equally to both of the currently approved DES?

Dr. Maisel said they had not seen any data suggesting the two are different in the off-label population.

d. Although diabetic patients were included in the randomized control trials submitted for DES approval, neither of the approved DES have a specific labeled indication for use in diabetics (either insulin-requiring or non-insulin requiring). Is there a DES thrombosis safety concern for this important high risk cardiovascular subgroup?

A panel member noted that an ongoing major trial, FREEDOM, will address this question. No panel member felt there was any specific concern with enough evidence to warrant making any recommendation other than that additional information is needed.

Dr. Maisel asked the panel members to address any problems with his summary of the panel's responses to question three. Dr. Hirshfeld said the big unanswered question is optimal duration. Dr. Brinker agreed and said physicians moved to prolonged antiplatelet prior to the AHA guidelines and have a gut feeling but no definitive data that higher risk patients may benefit from extended duration. Dr. Yancy emphasized that this is off-label and said there is a need for more data and new trials.

Dr. White agreed and proposed using "stent" rather than "drug-eluting stent" in the statement for 3(a) so as not to drive patients to choose bare metal stents. Dr. Somberg agreed with the need for more data and mentioned a dispute with CDER. Dr. Zuckerman said they are working with their colleagues in CDER and highlighted the point about getting a real drug trial. Dr. Somberg also raised the issue of stent thrombosis in those with optimum dual antiplatelet therapy and reminded everyone of various issues with clopidogrel. Dr. Page stressed that in 3(a) DES should be contraindicated if a patient is either unwilling or unable to maintain antiplatelet therapy. Dr. Kato also agreed and added to Dr. Somberg's comments that we are also dealing with an off-label use of clopidogrel.

Dr. Normand disagreed because she did not think it is a well-posed question and said that patients need to be given the choice of options and had not seen any data on other relevant options. Dr. Lindenfeld agreed with the statements and in particular with Dr. White regarding 3(a), but he said perhaps there should be a caveat that says only specific patient groups may benefit from one year. Dr. Laskey agreed but reminded everyone that the stent and drug must be viewed together. He also noted that the twelve month guideline was generally applied to a lower risk population. Dr. Morrison agreed in principle with Dr. Normand that the issue is compared to what. He agreed with the consensus of the panel and highlighted the data suggesting that DES are better in the acute STEMI population.

Dr. Topol disagreed with the idea of removing "drug-eluting" from 3(a) and said the evidence overall suggests an excess of late stent thrombosis for drug-eluting over bare metal stents in complex patients. Dr. Vetrovec suggested that while more complex

patients have higher risk regardless of the therapy, there is concern there may be a higher signal for DES. Dr. Weinberger agreed and underlined the critical importance of patient compliance with antiplatelet therapy.

Dr. Nissen said it was important not to convey that continuing clopidogrel past twelve months eliminates residual risk of DES. Dr. Harrington shared Dr. Normand's concern about inadequate evidence and agreed with Dr. Topol that the comments should be confined to drug-eluting stents. Dr. Edmunds agreed there is increased risk with DES in off-label patients and said the hazard continues. Dr. Domanski supported including all stents in 3(a) and supported a recommendation of at least twelve months of clopidogrel.

4. Given the currently available data and remaining areas of uncertainty, do the risks of stent thrombosis in the broad population of patients currently treated with DES in US clinical practice potentially outweigh the benefits (i.e., reduced repeat revascularization procedures) compared to the previous standard of care (e.g., medical therapy, BMS, CABG) such that the current DES labeling (indications, contraindications, warnings, precautions) should be modified?

Dr. Maisel proposed the following addition to the labeling for both stents, "Data outside these indications is limited. Use of the stent outside these indications may be associated with an increased risk of stent thrombosis, MI, and death." Dr. Zuckerman pointed out that the current labeling states that safety and effectiveness have not been established in certain populations which are listed. Some panel members thought it should be stated more strongly, but Dr. Maisel said a black box warning was far too strong considering the number of thoughtful physicians who choose to use the product off-label. One panel member agreed they would need more data and greater consensus for a black box warning. One panel member said the statement should take into consideration the better results with CABG, but another member was unsure that CABG is clearly better.

6. What long-term data need to be collected to help further define the risk of thrombosis in DES?

a. Should future premarket studies conducted to support approval of new DES be modified to better assess thrombosis risk?

b. Should the long-term follow-up of the pivotal trial cohorts and post-approval studies currently mandated by FDA be modified?

One panel member said information on patient compliance, a control group, and on availability of stent types and other therapies should be collected and proposed using parallel naturalistic studies. Another proposed a national registry of patients who have had a late stent thrombosis. He noted the data would be skewed but said it could be compared to those who have had a stent with no sequelae. Panel members generally supported moving in the direction of randomized clinical trials.

One panel member said there seems to be unwillingness to do appropriate trials of the conjunctive medical therapy and said information on the genomic underpinnings could be obtained by assembling patients who have suffered late stent thrombosis. Dr. Maisel asked if pre-market studies must be designed to demonstrate non-inferiority to already approved drug-eluting stents and at what time point. One panel member said to some extent yes and also voiced support for very long-term registries that have some comparator.

7. The optimal duration of dual-antiplatelet therapy in DES patients is undefined. Indefinite clopidogrel use may not prevent very late stent thrombosis, may expose patients to an unacceptable increased risk of bleeding, and has important economic considerations. Please comment specifically on the clinical study designs that would be most informative and yet feasible to evaluate this risk given current patterns of DES use and uncertainty regarding the optimal duration of dual antiplatelet therapy.

One panel member proposed looking at patients with fairly new stents and randomizing them to various durations of follow-up.

In summary, with regard to 6(a), Dr. Maisel said the consensus was yes and that they need to be larger, longer, and provide information on the risk for individual stents.

For 6(b) he said it was appropriate to follow the cohorts longer, patient and vessel characteristics must be understood, compliance must be assessed, there needs to be some control group, and studies need to be adequately powered. For 7 he proposed randomizing patients at twelve months to either discontinuation or continuation of clopidogrel as a possible alternative to a randomized trial looking at varying durations of clopidogrel.

Dr. Nissen said there should be a third study arm looking at bare metal with relatively short-term clopidogrel. Dr. Edmunds said that any new DES must be evaluated against CABG, not BMS, and that patients should be informed of ongoing thrombotic risk until it can be shown that the stented segment is lined with functional endothelial cells.

5. In addition to current FDA efforts, what patient and/or physician education or other outreach measures (i.e., Public Health Notification) could potentially reduce the risk of stent thrombosis?

One panel member suggested a Dear Doctor letter from FDA summarizing the take-home messages from the panel meeting.

Ms. Adams said there is no precedent for including off-label use data on the label and that there are liability issues associated with doing so. She also raised the issue of potential impact on sponsors conducting studies or awaiting approval. She reminded everyone that they were really advising FDA to take the spirit of the panel's concerns and frame them with respect to the agency's regulatory authority. Dr. Nissen proposed consideration of a patient guide.

Daniel Schultz, M.D., Director, CDRH, thanked the panel as well as all those in attendance. He said it is important to bring controversial issues to an open public forum.

He also noted the hard work done by FDA staff in putting the meeting together. He also thanked all of the speakers who presented data to the panel. He said FDA's review process works given the unanimous agreement that the approved, on-label use is still appropriate, that it is the agency's responsibility to provide updated information to patients and physicians, that they must continue to monitor the issue, that well deisgned studies should be encouraged to look at converting diverse medical practices to on-label indications when the data is available, and that there must be a strong commitment by FDA to a total life cycle approach.

ADJOURNMENT

Dr. Maisel thanked the FDA, the industry sponsors, speakers, and the panel members. He adjourned the meeting at 4:38 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel on December 8, 2006, and that these minutes accurately reflect what transpired.

James P. Swink
Executive Secretary

I approve the minutes of the December 8, 2006, meeting as recorded in this summary.

William H. Maisel, M.D., M.P.H.
Chairperson

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